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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/976,560	11/24/97	FREIMER	N UCAL-250-02U

EXAMINER	
ARTHUR, L	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/976,560	Freimer et al.
Examiner	**Group Art Unit**
Lisa Athur	1655

[X] Responsive to communication(s) filed on *Mar 22, 2000*

[ ] This action is **FINAL.**

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

[X] Claim(s) *1-12 and 17-24* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

[ ] Claim(s) _____ is/are allowed.

[X] Claim(s) *1-12 and 17-24* is/are rejected.

[ ] Claim(s) _____ is/are objected to.

[ ] Claims _____ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.

[ ] The specification is objected to by the Examiner.

[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [X] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____.

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

[ ] Notice of References Cited, PTO-892

[ ] Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

[ ] Interview Summary, PTO-413

[ ] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the paper filed March 22, 2000. Claims 13,15 and 16 have been canceled. Claims 8, 8-11,17,20 and 24 have been amended. Currently, claims 1-12 and 17-24 are pending. Prosecution on this application is being reopened in order to add new grounds of rejection. Any objections or rejections which have not been reiterated in this action from the previous action have been withdrawn.

MAINTAINED REJECTIONS

2. Claims 1-12, and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting an increased susceptibility for bipolar mood disorder by performing a pedigree analysis for the individual's family and analyzing the DNA from family members for linkage of markers on the short arm of chromosome 18 between and inclusive of SAVA5 and ga203, D18S1140 and ga203, SAVA5 and W3422, S18S1140 and W3422, D18S1140 and ta201 and S18S59 and ta201 , does not reasonably provide enablement for a method of detecting a bipolar mood disorder susceptibility polymorphism by detecting polymorphisms between and inclusive of SAVA5 and ga203 or any of the other recited markers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims, as written, are not commensurate in scope with the disclosure in the specification because the specification has not provided sufficient guidance in light of the

teachings in the art to enable the skilled artisan to detect a bipolar mood disorder susceptibility polymorphism without undue experimentation for the reasons which follow. The art teaches that a while linkage has been shown between several different chromosomal regions and bipolar mood disorder, a susceptibility locus for this disease has yet to be identified. Stine et al. (AM J. HUM GENET. (1995) 57:1384-1394) showed evidence of linkage between bipolar disorder and markers on the short art of chromosome 18, i.e. 18p including marker D18S59 (table 1) and showed a parent-of-origin effect operating in this disease, but acknowledged that the number of loci and their precise location require further study (page 1392, col. 2). McInnes et al. (PNAS (1996) 93:13060-13065) teach that interpreting results from linkage analysis of bipolar mood disorder and other behavioral phenotypes is very difficult and often misleading because behavioral phenotypes are difficult to define, as are etiologically heterogenous and there is a lack of knowledge as to the mode of transmission of these diseases. McInnes et al concluded that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for any psychiatric disorder (page 13060, col.2, paragraph 1). However, McInnes et al. Performed a genome screening analysis for possible genes associated with bipolar disorder and found suggestive lod scores in segments of 18q,18p and 11p (see abstract and Table 1) including marker D18S59. McInnes et al. states that the point of their study was to detect regions which merited further investigation (page 13063, col. 1, para. 1) and specifically identified the telomere of 18p as a region to further study (page 13064, col. 1, para 1). McInnes et al. States that genome screening is a first stage of a multi step process for identifying genes for complex traits (page

13064, col. 2, para. 2). McInnes et al. Taught that the second and third stages in their process were delineating clear candidate regions and fine mapping studies. Esterling et al. (MOLECULAR PSYCHIATRY (1997) 2:501-504) constructed a high resolution integrated map of 18p11.2 which is a 40cM region which they state contains a potential bipolar susceptibility locus (see Figure 1). However, even with these high resolution maps and linkage studies even as 1999 no specific polymorphisms or loci have been identified as a bipolar susceptibility locus. Ewald et al. (Psychiatric Genetics (1997) 7:1-12) teach that while chromosome 18 is one of the most promising chromosomes to contain a bipolar susceptibility locus, the research is still considered a search for susceptibility genes (see abstract). Gerson et al. (Neuropsychopharmacology (1998) 18(4): 233-242) reviewed the progress in identifying genes for manic-depressive illness and concluded that while chromosome 18 including the short arm of chromosome 18 is one of the best candidate locations for a bipolar susceptibility gene, and that the positive linkage results represent important progress, scientists are yet a long way from demonstrating disease mutations in bipolar illness (page 239, col. 2, para. 2, bottom). Nothen et al. (Molecular Psychiatry (1999) 4(1): 76-84) concluded as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may exist on chromosome 18, but does not provide a reasonable expectation as of yet that polymorphisms in the region of 18p is associated with a bipolar susceptibility locus or what that locus will be.

The specification teaches that the marker D18S59 showed the strongest evidence for linkage to bipolar disease (page 24-25) The specification then teaches that cloned human DNA

from this region, i.e. a 5cM region of chromosome 18 "is" assembled (page 25) . Markers within a 500kb and 300 kb subregion were used to delineate regions of bipolar susceptibility within the 5 cM 18pter region and blood from 105 affected individuals were tested for marker haplotypes. Figure 7 shows 18p allele frequencies and showed evidence of particular alleles being over represented on disease chromosomes. The comparisons in the figures were stated to show that the region of maximal sharing between affected individuals occur between 1140t and w3442 on chromosome 18 which is a region of about 300 kb. The specification then teaches that the sequences within these regions were then analyzed for expressed sequences and sequences which are associated with bipolar disorder. The specification teaches (starting at page 28) that a P1 clonal contig library should be made to identify candidate cDNAs which would then be sequenced and compared to nucleic acid data bases to identify a genes which may be a bipolar susceptibility gene. The cDNAs identified in the mapped to the minimal candidate region are then used as probes to screen the P1 phage contig library. This screening then identifies new microsatellite markers which are used to genotype the linkage disequilibrium sample. The cDNAs identified by these screens are then used to screen patient DNA for mutations, ie. polymorphisms associated with bipolar disorders.

The teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field as shown by the above analysis of the prior art

and because the specification has not provided evidence that would allow the skilled artisan to predict that where and what the bipolar susceptibility polymorphisms will be. The specification appears to present data defining a smaller region of the 18pter which has a higher probability of possibility containing a susceptibility locus but the art as of 1999 still states that scientist are a long way from pinpointing a locus or polymorphisms which are predictability associated with bipolar disease. The specification describes a research project for searching for polymorphisms that may exist in the defined region but the protocol described constitutes undue experimentation because the skilled artisan would be required to perform a large amount of essentially random screening of the defined region and would in no way be able to reasonably predict from the specification the identity of the polymorphisms associated with bipolar disease. Furthermore, the claims as written are claims to a research project without a predictable outcome because they encompass the detection of bipolar disease susceptibility polymorphisms. The art makes clear that this objective is of great interest and the target of extensive research by many groups. In fact many groups are taking the same approach as described in the specification for identifying such a bipolar locus without success. The fact that the specification presents evidence of linkage to the recited markers to a smaller region than is taught by the art would provide information within families of affected individuals such that an increased risk of developing bipolar mood disorder could be predicted in a particular family member by doing a pedigree analysis using the markers disclosed int he specification and recited in the claims showing maximal sharing between affected individuals. The specification however does enable the skilled artisan to detect a bipolar mood

disorder locus or polymorphisms within the recited region without undue experimentation for the reasons given above.

Response to Arguments

3. The response traverses the rejection on the following grounds. All of the arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. The response argues that the data in the instant invention is based upon population studies, while the cited references have based their studies on unrelated families. This argument has been thoroughly reviewed but is not persuasive because the references were cited to establish the general unpredictability in correlating a polymorphism to bipolar disease. The fact that this instant invention is based upon pedigree-based studies makes the linkage of the defined region to bipolar disease in a family predictable, the data in the specification do not enable the skilled artisan to predictably identify polymorphisms in that region which are associated with bipolar disease because there is no evidence provided as to what those polymorphisms might be.

The response argues that applicants have in fact identified polymorphism associated with bipolar mood disorder. Specifically, the response asserts that D18S59 is a polymorphic marker and that an allele size of 154 base pairs at D18S59 is linked to BP. The response also asserts that the 154 base allele size at D18S59 is associated with a reduced susceptibility to bipolar disease. The response also states that an allele size of 271 at marker D18S476 is associated with bipolar disease. This argument has been thoroughly reviewed but is deemed non-persuasive for the reasons which follow. First, the crux of the rejection is based upon the ambiguous and broad

meaning of the term "bipolar mood disorder susceptibility polymorphism". This term has been interpreted by the Office to mean a particular sequence of nucleotides or a nucleotide which is detected in individuals which are susceptible to bipolar mood disorder. However, the response argues that the presence of an allele size of 154 based pairs when hybridized with the known polymorphic marker D18S59 is indicative of a reduced susceptibility to bipolar disease. These arguments appear to be implying that the D18S59 marker can be used on any individual to screen chromosome 18 between SAVA5 and ga203 and that if a 154 base pair fragment is detected that individual has a reduced risk for bipolar disease. However, all that the specification has shown is that within a pedigree this size fragment appears to be over represented. It should be noted that the specification does not teach that the 154 base pair allele in indicative of a reduced susceptibility to bipolar disease. The specification has established that a bipolar mood disorder susceptibility can be detected in a family member by hybridizing with a microsatellite allele that hybridizes to the region of chromosome 18 between SAVA5 and ga203 and then comparing the results with a family member known to have bipolar disease. The specification has not, however, identified polymorphisms in the region between SAVA5 and ga203 which can be detected in any individual and which are generally associated with bipolar disease. The term "bipolar susceptibility polymorphism" encompasses mutations within a bipolar disease gene and other mutations which when present indicate disease susceptibility. Clearly, such mutations have not been identified. The markers described in the specification are not in and of themselves bipolar mood disorder susceptibility polymorphisms because these markers are polymorphic sequences

which are found through out the genome and are not specific to this described region of chromosome 18 but are instead used to indicate the presence of the nucleic acid between the described markers which appears to be over represented in individuals with bipolar disease.

NEW GROUNDS OF REJECTION

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The essential element of the claimed invention is an association between a polymorphism in the region of chromosome 18 between markers SAVA5 and ga203 and bipolar mood disorder. The specification shows by analysis of a large pedigree that linkage disequilibrium exists at the short arm of chromosome 18 between markers SAVA5 and ga203 and that the DNA between these markers is over represented in individuals with bipolar mood disorder. The specification teaches that several known microsatellite polymorphic markers produce particular allele sizes when hybridized with the region between SAVA5 and ga203 on chromosome 18. However, the

specification contains no description of specific polymorphisms in this region which are generally indicative of a susceptibility to bipolar mood disorder because the specification only teaches that in a pedigree analysis the region between SAVA5 and ga203 on chromosome 18 is over represented in individuals in the pedigree who have bipolar mood disorder. A polymorphism includes point mutations, small deletions, insertions within and around a bipolar disease locus none of which have been described in the specification. Instead the specification only described a linkage analysis of known markers in phenotypically diagnosed bipolar in families. This linkage does not support the genus of claimed methods for detecting bipolar mood disorder susceptibility polymorphisms because the disclosed studies do not teach a representative number of species of the genus of polymorphisms encompassed by the claims. There are so many genetic variations which are inherited from family members that would have absolutely no association with bipolar mood disorder and only a few which might be associated with bipolar disease. As set forth by the Court in *Vas Cath Inc. v. Mahurkar*, 19 USPQ2d 111, the written description must convey to one of skill in the art "the reasonable clarity" that as of the filing date, applicant was in possession of the claimed invention. Absent a written description disclosing a representative number of species of polymorphisms associated with a susceptibility to bipolar mood disorder, the specification fails to show that applicant was, in fact, "in possession of the claimed invention" at the time the application for patent was filed.

6. No claims are allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday-Wednesday from 7:00AM to 2:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

June 26, 2000